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Sequence Listing was accepted.

See attached Validation Report.

If you need help call the Patent Electronic Business Center at (866)  
217-9197 (toll free).

Reviewer: markspencer

Timestamp: [year=2008; month=10; day=10; hr=9; min=32; sec=25; ms=908; ]

=====

Application No: 10658834 Version No: 5.0

Input Set:

Output Set:

**Started:** 2008-08-27 18:29:50.675  
**Finished:** 2008-08-27 18:30:41.822  
**Elapsed:** 0 hr(s) 0 min(s) 51 sec(s) 147 ms  
**Total Warnings:** 198  
**Total Errors:** 88  
**No. of SeqIDs Defined:** 1306  
**Actual SeqID Count:** 1306

Error code	Error Description
W 213	Artificial or Unknown found in <213> in SEQ ID (2)
W 213	Artificial or Unknown found in <213> in SEQ ID (3)
W 213	Artificial or Unknown found in <213> in SEQ ID (4)
W 213	Artificial or Unknown found in <213> in SEQ ID (5)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (5)
W 213	Artificial or Unknown found in <213> in SEQ ID (6)
W 213	Artificial or Unknown found in <213> in SEQ ID (7)
W 213	Artificial or Unknown found in <213> in SEQ ID (8)
W 213	Artificial or Unknown found in <213> in SEQ ID (9)
W 213	Artificial or Unknown found in <213> in SEQ ID (10)
W 213	Artificial or Unknown found in <213> in SEQ ID (11)
W 213	Artificial or Unknown found in <213> in SEQ ID (12)
W 213	Artificial or Unknown found in <213> in SEQ ID (13)
W 213	Artificial or Unknown found in <213> in SEQ ID (14)
W 213	Artificial or Unknown found in <213> in SEQ ID (15)
W 213	Artificial or Unknown found in <213> in SEQ ID (16)
W 213	Artificial or Unknown found in <213> in SEQ ID (17)
W 213	Artificial or Unknown found in <213> in SEQ ID (18)
E 355	Empty lines found between the amino acid numbering and the

**Input Set:**

**Output Set:**

**Started:** 2008-08-27 18:29:50.675  
**Finished:** 2008-08-27 18:30:41.822  
**Elapsed:** 0 hr(s) 0 min(s) 51 sec(s) 147 ms  
**Total Warnings:** 198  
**Total Errors:** 88  
**No. of SeqIDs Defined:** 1306  
**Actual SeqID Count:** 1306

Error code	Error Description
E 321	No. of Bases conflict, this line has no nucleotides SEQID (18)
W 213	Artificial or Unknown found in <213> in SEQ ID (19)
W 213	Artificial or Unknown found in <213> in SEQ ID (20)
W 213	Artificial or Unknown found in <213> in SEQ ID (21) This error has occurred more than 20 times, will not be displayed
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (44)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (63)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (84)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (97)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (105)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (149)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (188)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (237)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (238)

**Input Set:**

**Output Set:**

**Started:** 2008-08-27 18:29:50.675  
**Finished:** 2008-08-27 18:30:41.822  
**Elapsed:** 0 hr(s) 0 min(s) 51 sec(s) 147 ms  
**Total Warnings:** 198  
**Total Errors:** 88  
**No. of SeqIDs Defined:** 1306  
**Actual SeqID Count:** 1306

Error code	Error Description
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (274)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (332)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (377)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (386)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (441)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (478)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (522)
E 355	Empty lines found between the amino acid numbering and the
E 321	No. of Bases conflict, this line has no nucleotides SEQID (533)
E 355	Empty lines found between the amino acid numbering and the proteins
E 321	No. of Bases conflict, this line has no nucleotides SEQID (564) POS (112)

# SEQUENCE LISTING

<110> Gantier, Rene  
Guyon, Thierry  
Drittanti, Lila  
Vega, Manuel

<120> RATIONAL EVOLUTION OF CYTOKINES FOR HIGHER STABILITY, THE CYTOKINES AND ENCODING NUCLEIC ACID MOLECULES

<130> 119365-00005/922

<140> 10658834

<141> 2003-09-08

<150> 60/457,135

<151> 2003-03-21

<150> 60/409,898

<151> 2002-09-09

<160> 1306

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 165

<212> PRT

<213> Homo sapiens

<400> 1

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Leu	Leu	Ala	Gln	Met	Arg	Arg	Ile	Ser	Leu	Phe	Ser	Cys	Leu	Lys	Asp
			20					25					30		
Arg	His	Asp	Phe	Gly	Phe	Pro	Gln	Glu	Glu	Phe	Gly	Asn	Gln	Phe	Gln
			35				40					45			
Lys	Ala	Glu	Thr	Ile	Pro	Val	Leu	His	Glu	Met	Ile	Gln	Gln	Ile	Phe
			50			55					60				
Asn	Leu	Phe	Ser	Thr	Lys	Asp	Ser	Ser	Ala	Ala	Trp	Asp	Glu	Thr	Leu
65					70					75					80
Leu	Asp	Lys	Phe	Tyr	Thr	Glu	Leu	Tyr	Gln	Gln	Leu	Asn	Asp	Leu	Glu
				85					90					95	
Ala	Cys	Val	Ile	Gln	Gly	Val	Gly	Val	Thr	Glu	Thr	Pro	Leu	Met	Lys
				100				105					110		
Glu	Asp	Ser	Ile	Leu	Ala	Val	Arg	Lys	Tyr	Phe	Gln	Arg	Ile	Thr	Leu
			115				120					125			
Tyr	Leu	Lys	Glu	Lys	Lys	Tyr	Ser	Pro	Cys	Ala	Trp	Glu	Val	Val	Arg
			130			135					140				
Ala	Glu	Ile	Met	Arg	Ser	Phe	Ser	Leu	Ser	Thr	Asn	Leu	Gln	Glu	Ser
145					150					155					160
Leu	Arg	Ser	Lys	Glu											
				165											

<210> 2

<211> 165

<212> PRT

<213> Artificial Sequence

<220>

<223> D2A Mutant IFN-alpha 2b

<400> 2

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 1          5          10          15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
          20          25          30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
          35          40          45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
          50          55          60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65          70          75          80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
          85          90          95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
          100          105          110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
          115          120          125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
          130          135          140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145          150          155          160
Leu Arg Ser Lys Glu
          165
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<210> 3

<211> 165

<212> PRT

<213> Artificial Sequence

<220>

<223> P4A Mutant IFN-alpha 2b

<400> 3

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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
          20          25          30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
          35          40          45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
          50          55          60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65          70          75          80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
          85          90          95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
          100          105          110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
          115          120          125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
          130          135          140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
```

145                      150                      155                      160  
 Leu Arg Ser Lys Glu  
                          165  
 <210> 4  
 <211> 165  
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 <213> Artificial Sequence  
  
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 <223> Q5A Mutant IFN-alpha 2b  
  
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 Cys Asp Leu Pro Ala Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met  
   1                          5                          10                          15  
 Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp  
                           20                          25                          30  
 Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln  
                           35                          40                          45  
 Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe  
   50                          55                          60  
 Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu  
  65                          70                          75                          80  
 Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu  
                           85                          90                          95  
 Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys  
                          100                         105                         110  
 Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu  
                          115                         120                         125  
 Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg  
  130                         135                         140  
 Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser  
 145                      150                      155                      160  
 Leu Arg Ser Lys Glu  
                          165

<210> 5  
 <211> 165  
 <212> PRT  
 <213> Artificial Sequence

<220>

<223> T6A Mutant IFN-alpha 2b

<400> 5  
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 Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp  
                           20                          25                          30  
 Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln  
                           35                          40                          45  
 Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe  
   50                          55                          60  
 Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu  
  65                          70                          75                          80  
 Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu  
                           85                          90                          95  
 Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys

100	105	110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu		

115	120	125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg		
130	135	140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser		
145	150	155
Leu Arg Ser Lys Glu		160

165

<210> 6

<211> 165

<212> PRT

<213> Artificial Sequence

<220>

<223> H7A Mutant IFN-alpha 2b

<400> 6

Cys Asp Leu Pro Gln Thr Ala Ser Leu Gly Ser Arg Arg Thr Leu Met		
1	5	10
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp		15
20	25	30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln		
35	40	45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe		
50	55	60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu		
65	70	75
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu		
85	90	95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys		
100	105	110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu		
115	120	125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg		
130	135	140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser		
145	150	155
Leu Arg Ser Lys Glu		160

165

<210> 7

<211> 165

<212> PRT

<213> Artificial Sequence

<220>

<223> S8A Mutant IFN-alpha 2b

<400> 7

Cys Asp Leu Pro Gln Thr His Ala Leu Gly Ser Arg Arg Thr Leu Met		
1	5	10
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp		15
20	25	30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln		
35	40	45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe		



50		55		60											
Asn	Leu	Phe	Ser	Thr	Lys	Asp	Ser	Ser	Ala	Ala	Trp	Asp	Glu	Thr	Leu
65					70				75						80
Leu	Asp	Lys	Phe	Tyr	Thr	Glu	Leu	Tyr	Gln	Gln	Leu	Asn	Asp	Leu	Glu
			85						90					95	
Ala	Cys	Val	Ile	Gln	Gly	Val	Gly	Val	Thr	Glu	Thr	Pro	Leu	Met	Lys
		100						105					110		
Glu	Asp	Ser	Ile	Leu	Ala	Val	Arg	Lys	Tyr	Phe	Gln	Arg	Ile	Thr	Leu
	115						120					125			
Tyr	Leu	Lys	Glu	Lys	Lys	Tyr	Ser	Pro	Cys	Ala	Trp	Glu	Val	Val	Arg
	130					135					140				
Ala	Glu	Ile	Met	Arg	Ser	Phe	Ser	Leu	Ser	Thr	Asn	Leu	Gln	Glu	Ser
145					150					155					160
Leu	Arg	Ser	Lys	Glu											
				165											

<210> 8

<211> 165

<212> PRT

<213> Artificial Sequence

<220>

<223> L9A Mutant IFN-alpha 2b

<400> 8

Cys	Asp	Leu	Pro	Gln	Thr	His	Ser	Ala	Gly	Ser	Arg	Arg	Thr	Leu	Met
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Leu	Leu	Ala	Gln	Met	Arg	Arg	Ile	Ser	Leu	Phe	Ser	Cys	Leu	Lys	Asp
		20						25				30			
Arg	His	Asp	Phe	Gly	Phe	Pro	Gln	Glu	Glu	Phe	Gly	Asn	Gln	Phe	Gln
	35					40					45				
Lys	Ala	Glu	Thr	Ile	Pro	Val	Leu	His	Glu	Met	Ile	Gln	Gln	Ile	Phe
	50					55					60				
Asn	Leu	Phe	Ser	Thr	Lys	Asp	Ser	Ser	Ala	Ala	Trp	Asp	Glu	Thr	Leu
65					70				75						80
Leu	Asp	Lys	Phe	Tyr	Thr	Glu	Leu	Tyr	Gln	Gln	Leu	Asn	Asp	Leu	Glu
			85						90					95	
Ala	Cys	Val	Ile	Gln	Gly	Val	Gly	Val	Thr	Glu	Thr	Pro	Leu	Met	Lys
		100						105					110		
Glu	Asp	Ser	Ile	Leu	Ala	Val	Arg	Lys	Tyr	Phe	Gln	Arg	Ile	Thr	Leu
	115						120					125			
Tyr	Leu	Lys	Glu	Lys	Lys	Tyr	Ser	Pro	Cys	Ala	Trp	Glu	Val	Val	Arg
	130					135					140				
Ala	Glu	Ile	Met	Arg	Ser	Phe	Ser	Leu	Ser	Thr	Asn	Leu	Gln	Glu	Ser
145					150					155					160
Leu	Arg	Ser	Lys	Glu											
				165											

<210> 9

<211> 165

<212> PRT

<213> Artificial Sequence

<220>

<223> G10A Mutant IFN-alpha 2b

<400> 9

Cys Asp Leu Pro Gln Thr His Ser Leu Ala Ser Arg Arg Thr Leu Met  
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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp  
20 25 30  
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln  
35 40 45  
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe  
50 55 60  
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu  
65 70 75 80  
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu  
85 90 95  
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys  
100 105 110  
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu  
115 120 125  
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg  
130 135 140  
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser  
145 150 155 160  
Leu Arg Ser Lys Glu  
165

<210> 10

<211> 165

<212> PRT

<213> Artificial Sequence

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<223> S11A Mutant IFN-alpha 2b

<400> 10

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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp  
20 25 30  
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln  
35 40 45  
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe  
50 55 60  
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu  
65 70 75 80  
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu  
85 90 95  
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys  
100 105 110  
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu  
115 120 125  
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg  
130 135 140  
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser  
145 150 155 160  
Leu Arg Ser Lys Glu  
165

<210> 11

<211> 165  
<212> PRT  
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<220>  
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1 5 10 15  
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp  
20 25 30  
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln  
35 40 45  
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe  
50 55 60  
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu  
65 70 75 80  
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu  
85 90 95  
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys  
100 105 110  
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu  
115 120 125  
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg  
130 135 140  
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser  
145 150 155 160  
Leu Arg Ser Lys Glu  
165

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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp  
20 25 30  
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln  
35 40 45  
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe  
50 55 60  
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu  
65 70 75 80  
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu  
85 90 95  
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys  
100 105 110  
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu  
115 120 125  
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg

130

135

140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn